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Original article

Prediction of inactive disease in juvenile idiopathic arthritis: a multicentre observational cohort study

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Abstract

Objectives. To predict the occurrence of inactive disease in JIA in the first 2 years of disease.

Methods. An inception cohort of 152 treatment-naïve JIA patients with disease duration <6 months was analysed. Potential predictors were baseline clinical variables, joint US, gut microbiota composition and a panel of inflammation-related compounds in blood plasma. Various algorithms were employed to predict inactive disease according to Wallace criteria at 6-month intervals in the first 2 years. Performance of the models was evaluated using the split-cohort technique. The cohort was analysed in its entirety, and separate models were developed for oligoarticular patients, polyarticular RF negative patients and ANA positive patients.

Results. All models analysing the cohort as a whole showed poor performance in test data [area under the curve (AUC): <0.65]. The subgroup models performed better. Inactive disease was predicted by lower baseline juvenile arthritis DAS (JADAS)-71 and lower relative abundance of the operational taxonomic unit *Mogibacteriaceae* for oligoarticular patients (AUC in test data: 0.69); shorter duration of morning stiffness, higher haemoglobin and lower CXCL-9 levels at baseline for polyarticular RF negative patients (AUC in test data: 0.69); and shorter duration of morning stiffness and higher baseline haemoglobin for ANA positive patients (AUC in test data: 0.72).

Conclusion. Inactive disease could not be predicted with satisfactory accuracy in the whole cohort, likely due to disease heterogeneity. Interesting predictors were found in more homogeneous subgroups. These need to be validated in future studies.

Key words: juvenile idiopathic arthritis, prediction, inactive disease, CXCL-9, gut microbiota

CLINICAL SCIENCE

Rheumatology key messages

- Inactive disease could not be predicted with satisfactory accuracy in JIA patients.
- Interesting predictors were found in JIA disease subgroups that need validation in future studies.
- Better characterization of homogeneous subgroups could improve the understanding of the prognosis of JIA.

Introduction

JIA is an umbrella term covering chronic arthritis of unknown cause lasting for >6 weeks with an onset before 16 years of age [1]. The prognosis of children with JIA has improved considerably over the past decades. Following the advent of MTX and biologic agents, many children achieve disease remission within a reasonable time frame [2–5]. Nevertheless, there is still a substantial proportion of children who do not achieve inactive disease, or fail to do so within a short period of time. Prolonged disease activity causes distress, diminishes the overall well-being of the child and is associated with a higher risk of long term sequelae of the disease, including irreversible

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joint damage [6–10]. On top of this, in adult RA, better outcomes are achieved if effective treatment is started early in the course of disease, the so-called window of opportunity [11–15]. Even though JIA differs substantially from adult RA in terms of clinical presentation and prognosis, such a window of opportunity might also be present in paediatric rheumatology.

For various reasons, it is not feasible to prescribe biologic agents to all children with JIA. First, this would expose many children to the potential side effects of the drugs and, secondly, this practice would be too costly. Moreover, not all children need biologic agents, since some respond well to intra-articular corticosteroid injections only, or failing that strategy, may benefit from the addition of MTX [16].

Therefore, since all children should receive early and effective treatment and not all children should be prescribed biologic agents, there is a clinical need of predictors capable of stratifying JIA patients according to their prognosis, thus enabling identification early in the course of disease, ideally at the time of diagnosis, of those patients in need of more aggressive therapy. A review of the literature revealed that it is unlikely that clinical predictors suffice to achieve that goal [17]. This conclusion was challenged by a recently published clinical prediction model that performed well in test data [18]. However, its performance was poor in our cohort. Therefore, other categories of predictors need to be taken into consideration for the accurate prediction of the prognosis of JIA.

Our aim was to construct a prediction model of the prognosis of JIA patients in a well-defined, multicentre cohort, using clinical, imaging and microbiota data as well as a panel of inflammation-related compounds in blood plasma.

Methods

We performed a prospective, observational cohort study at the Istituto Giannina Gaslini (IGG, Genoa, Italy), Ospedale Pediatrico Bambino Gesù (OPBG, Rome, Italy) and the Wilhelmina Children's Hospital (WKZ, Utrecht, The Netherlands), between October 2013 and December 2015 (IGG and OPBG) and between March 2014 and December 2015 (WKZ). The study was approved by the local medical ethics committees of the Istituto Giannina Gaslini in Genoa, the Ospedale Pediatrico Bambino Gesù in Rome and the Wilhelmina Children's Hospital in Utrecht and all participating patients or their parents (where appropriate) provided written informed consent prior to participation. The study was conducted according to good clinical practice guidelines and the Declaration of Helsinki.

Consecutive patients with JIA according to International League Against Rheumatism criteria [19] at disease onset (onset of symptoms at most 6 months before enrolment) who had not started any treatment other than NSAIDs were eligible for enrolment. Systemic JIA patients were not included.

At baseline, clinical parameters regarding demographics and disease manifestations were collected and routine laboratory examinations were performed. The childhood health assessment questionnaire was completed by the child or the parents. Information about ongoing treatment (NSAIDs) was collected. An additional sample of blood was collected, and peripheral blood plasma was isolated and frozen at −80°C. These samples were then shipped to WKZ on dry ice by overnight shipment to perform an in-house developed and validated (ISO9001 certified) multiplex immunoassay (Laboratory of Translational Immunology, University Medical Centre Utrecht) based on Luminex technology (xMAP, Luminex, Austin, TX, USA). The assay was performed as described previously [20]. Aspecific heterophilic immunoglobulins were pre-absorbed from all samples with heteroblock (Omega Biologicals, Bozeman, MT, USA). Acquisition was performed with the Bio-Rad FlexMAP3D (Bio-Rad laboratories, Hercules, CA, USA) in combination with xPONENT software version 4.2 (Luminex). Data were analysed by five-parametric curve fitting using Bio-Plex Manager software, version 6.1.1 (Bio-Rad).

Additionally, a stool sample for gut microbiota determination was collected and frozen at −80°C. These samples were shipped to OPBG on dry ice by overnight shipment for 16S bacterial ribosomal RNA pyrosequencing, as described in literature [21]. Reads were analysed by QIIME v.1.8.0, grouped into operational taxonomic units (OTUs) at a sequence similarity level of 97% [22–25] (Van Dijkhuizen *et al.* manuscript in preparation).

Finally, an extended joint ultrasonography was performed using a pre-specified protocol. Details of the protocol have been published previously [26]. All available covariates are listed in supplementary Table S1, available at *Rheumatology* online.

Enrolled patients were evaluated every 6 months and additionally in the case of a relapse, for 2 years or until the end of the study period in February 2017, whichever was first. At each visit, disease activity was assessed using the Wallace criteria for inactive disease [27]. Ongoing treatment was categorized as: no treatment; intra-articular joint injections with or without NSAIDs; MTX with or without oral steroids; and biological agents.

Statistical analysis

To assess the predictive performance of the Luminex and microbiota data over clinical data only, three different prediction models were developed, one consisting of clinical (including US) data only, one containing clinical and microbiota data, and one using clinical and Luminex data. All described models included treatment and the interval of time elapsed between baseline and the follow-up visits as covariates. The outcome was inactive disease *versus* active disease for all models. Missing clinical data were imputed by multiple imputations using chained equations producing 10 imputed datasets [28]. All other clinical variables, including the outcome, were used in the imputations, provided they were not linearly related to the variables to be imputed [28]. Missing microbiota and Luminex data were only due to missing samples in our cohort and were therefore not imputed.

The cohort was split at random into two-thirds for model training and one-third for model validation. To eliminate the influence of the data split on the model evaluation, the split was performed 10 times and the model was trained and tested in each of these split datasets. The performance was summarized as the mean over the 10 splits.

In the training data, univariate variable selection was performed by fitting a model and retaining the variables with a $P < 0.1$, or $P < 0.2$ in cases in which no variable had a $P < 0.1$. If variables correlated in training data (Spearman's $|\rho| > 0.6$), the variable with the lowest *P*-value was retained. The remaining variables were pooled in a multivariable model in the training data and this model was subsequently applied to the test data.

Several different algorithms were tried and model performance was assessed in an appropriate manner for each algorithm. In the primary analysis, to exploit the information contained in all visits for all patients, a repeated measurements analysis using generalized estimating equations (GEE) was performed [29, 30]. Performance of this model was tested using an area under the curve (AUC)-like statistic, adapted to models with repeated measurements [31].

Secondary analyses

Various secondary analyses were performed, including Cox proportional hazards models of time to first inactive disease and Cox regressions of time to inactive disease, using recurrent events analysis [32]. The performance of these models was assessed by predicting the risk score of patients in the test data and correlating this risk score with the observed outcome in the test dataset, using Somer's D correlation, adapted to censored data [33, 34], from which the *c*-statistic (similar to the AUC) was calculated.

Moreover, next to the longitudinal approach, the outcomes at 6 and 12 months after baseline were analysed separately. This approach opened up the possibility of applying more algorithms: we fitted logistic regression models, random forests and support vector machines. Performance of these models was assessed by calculating the AUC.

Finally, to reduce the heterogeneity of JIA, we fitted models to the groups of oligoarticular patients, polyarticular RF negative patients and ANA positive patients separately. Patients were pragmatically considered ANA positive, if they had at least one positive ANA determination at baseline (titre $\geqslant$1:160). Statistical analyses were carried out using R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 169 enrolled patients, 10 were enrolled after the start of MTX and seven were lost to follow-up (i.e. no follow-up data collected at all), leaving 152 patients to be analysed. Luminex data were available for 121 patients and gut microbiota data for 91 patients (supplementary Table S2, available at *Rheumatology* online). Missing Luminex and microbiota data were due to difficulties in the collection or shipment of samples and were unrelated to disease characteristics. Blood samples for Luminex analysis were collected in EDTA tubes at OPBG (compared with sodium heparin tubes at IGG and WKZ). Consequently, the Luminex results of OPBG patients were incomparable with those of the remainder of patients (data not shown). Therefore, the Luminex results of OPBG patients were excluded from the analysis. Thus, the clinical models were developed in 152 patients, contributing 508 visits, the microbiota models in 91 patients contributing 310 visits and the Luminex models in 80 patients contributing 261 visits.

Baseline characteristics are shown in Table 1. The majority of patients were female, presented with four active joints or fewer and continued to have persistent oligoarthritis. Almost 90% of patients with oligoarticular disease onset and all patients with polyarticular onset presented with high disease activity, according to the cut-off points of the juvenile arthritis disease activity score (JADAS)-71 [35]. Most patients achieved inactive disease during follow-up, but a substantial minority (about 20–40%) showed active disease at the follow-up visits (Table 2).

Primary analysis

The best GEE model for all patients combined is presented in supplementary Table S3, available at *Rheumatology* online, showing poor performance in test data (AUC: 0.65).

Secondary analyses

The results of the Cox models for time to first remission, Cox models with recurrent events, and the logistic regression at 6 and 12 months are shown in supplementary Tables S4–S7, available at *Rheumatology* online. All models, as well as the random forest and support vector machine algorithms (data not shown), performed poorly in test data.

Improved results were obtained when fitting a GEE model to the oligoarticular patients, polyarticular RF negative patients and ANA positive patients separately. For oligoarticular patients, the best model was the model with clinical and microbiota predictors. The odds of achieving inactive disease were decreased by a higher JADAS-71 score at baseline and higher relative abundance of the OTU *Mogibacteriaceae*. Other variables were associated in univariate analysis, but lost significance in the multivariable model (Table 3). The mean AUC over the imputed datasets was 0.79 in training data and 0.69 in test data (compared with 0.65 for the model with clinical variables only).

The best model for the polyarticular RF negative patients was the model with clinical and Luminex predictors. Among the variables associated in univariate analysis, the haemoglobin level and the ESR were correlated (Spearman's $\rho = -0.71$), and therefore the ESR was excluded. Likewise, the chemokine CXCL-9 correlated with soluble VEGF receptor 1 (sVEGF-R1; Spearman's $\rho = 0.88$), and therefore sVEGF-R1 was excluded. The multivariable model is shown in Table 4. The odds of

achieving inactive disease were decreased by a longer duration of morning stiffness, lower haemoglobin levels and higher CXCL-9 levels at baseline (supplementary Fig. S1, available at *Rheumatology* online). The mean AUC over the imputed datasets was 0.79 in training data and 0.69 in test data (marginally higher than the model with clinical predictors only, which had an AUC of 0.67). CXCL-9 was subsequently dichotomized. The best cut-off was at 30 pg/ml (supplementary Fig. S1, available at *Rheumatology* online), yielding an AUC of 0.78 in training data and 0.69 in test data. The sensitivity of this cut-off to predict patients achieving inactive disease at maximally 50% of follow-up visits was 0.31. The specificity was 0.94.

Finally, for the ANA positive patients, the best model was the clinical model (Table 5). The odds of achieving inactive disease were decreased by a duration of morning stiffness >2 h and lower haemoglobin levels at baseline. The mean AUC over the imputed datasets was 0.79 in training data and 0.72 in test data.

The predicted probabilities of inactive disease according to the three models as a function of the significant predictors are illustrated in Fig. 1.

Table 1 Baseline characteristics

	n = 152
Baseline variables	
Female, *n* (%)	112 (73.7)
Age at onset, median (IQR)	4.0 (2.1–7.8)
Disease duration, median (IQR)	0.2 (0.2–0.3)
Age at diagnosis/enrolment, median (IQR)	4.3 (2.4–8.2)
Active joints, median (IQR)	2 (1, 5)
More than four active joints, *n* (%)	43 (28.3)
JADAS-71, median (IQR)	13.2 (8.2–18.6)
ANA positive, *n* (%)[a]	84 (55.3)
RF positive, *n* (%)[a]	2 (1.3)
Uveitis, *n* (%)	8 (5.3)
Luminex data, *n* (%)	121 (79.6)
Gut microbiota data, *n* (%)	91 (59.9)
ILAR category at 6 months' follow-up	
Oligoarthritis persistent, *n* (%)	90 (59.2)
Oligoarthritis extended, *n* (%)	5 (3.3)
Polyarthritis RF positive, *n* (%)	2 (1.3)
Polyarthritis RF negative, *n* (%)	43 (28.3)
PsA, *n* (%)	5 (3.3)
ERA, *n* (%)	4 (2.6)
Undifferentiated arthritis, *n* (%)	3 (2.0)

[a]Missing clinical variables were imputed: ANA, *n* = 6; JADAS-71, *n* = 10; RF, *n* = 33. ILAR: International League Against Rheumatism; JADAS: juvenile arthritis DAS.

Discussion

The aim of this study was to develop a prediction model for the prognosis of JIA patients in the first 2 years of disease. The strength of the study was that we collected clinical, imaging, microbiota and Luminex data in a well-defined cohort of treatment-naïve JIA patients at onset. The prognostic value of these variables has never been analysed before. We employed a large number of statistical algorithms, taking a longitudinal approach by incorporating outcome information of all visits, as well as performing survival analysis and cross-sectional analyses at 6 and 12 months after diagnosis and initiation of treatment. Moreover, machine learning algorithms such as random forest and support vector machines were used. Nevertheless, we were unable to construct a prediction model with satisfying accuracy in the prediction of inactive disease according to Wallace criteria, in all patients together.

Despite the failure to develop a model in all patients together, we were able to generate prediction models for oligoarticular, polyarticular RF negative and ANA positive patients separately, even though the performance in test data was still only moderate (AUC: 0.69–0.72). For the oligoarticular patients, the odds of attaining inactive disease decreased following a higher JADAS-71 score and higher relative abundance of the OTU *Mogibacteriaceae* at baseline (Table 3). For polyarticular RF negative patients, the odds of inactive disease decreased following a longer duration of morning stiffness, lower haemoglobin levels and higher CXCL-9 levels at baseline (Table 4). Similarly, the odds of inactive disease decreased following a duration of morning stiffness >2 h and lower haemoglobin levels at baseline, for ANA positive patients (Table 5).

Table 2 Observed disease activity status according to Wallace criteria in the entire cohort and the three main subgroups

Time point	Entire cohort		Oligoarticular		Polyarticular RF negative		ANA positive	
	N	ID, *n* (%)	*N*	ID, *n* (%)	*N*	ID, *n* (%)	*N*	ID, *n* (%)
6 months	151	89 (58.9)	51	34 (66.7)	29	14 (48.3)	87	49 (56.3)
12 months	139	103 (74.1)	47	36 (76.6)	27	18 (66.7)	81	58 (71.6)
18 months	110	87 (79.1)	41	34 (82.9)	23	17 (73.9)	64	51 (79.7)
24 months	82	61 (74.4)	31	24 (77.4)	16	10 (62.5)	53	45 (84.9)
Additional flare visits	26	0 (0)	9	0 (0)	5	0 (0)	13	0 (0)

ID: inactive disease.

Table 3 Best performing GEE model oligoarticular patients ($n = 52$)

Parameter	Visits ($m = 179$)	OR (95% CI)	Wald *P*-value
Intercept		2.79 (0.37, 21.10)	0.99
Duration of morning stiffness			
None or <15 min	105 (58.7)	Reference category	
15 min to 2 h	49 (27.4)	1.28 (0.38, 4.27)	0.69
>2 h	25 (14.0)	0.26 (0.05, 1.45)	0.12
Knee involvement (count)		0.67 (0.29, 1.53)	0.34
JADAS-71		0.89 (0.80, 0.997)	0.04
Christensenella		0.85 (0.69, 1.04)	0.11
Mogibacteriaceae		0.82 (0.68, 0.98)	0.03
Therapy during follow-up			
None	53 (29.6)	Reference category	
IACI ± NSAIDs	43 (24.0)	2.35 (0.78, 7.05)	0.13
MTX ± steroids or biologic agents	83 (46.4)	2.60 (0.81, 8.32)	0.11
Interval between baseline and visit, *y*		2.31 (0.89, 5.96)	0.08
AUC-like statistic			
	Minimum	**Mean**	**Maximum**
Training data	0.79	0.79	0.79
Test data	0.69	0.69	0.70

Included variables showed a univariate $P < 0.1$ and no bivariate correlations (Spearman's $|\rho| \leqslant 0.6$). AUC: area under the curve; GEE: generalised estimating equations; IACI: intra-articular corticosteroid injections; JADAS: juvenile arthritis DAS; m: number of visits; n: number of patients.

Table 4 Best performing GEE model polyarticular RF negative patients ($n = 29$)

Parameter	Visits ($m = 100$)	OR (95% CI)	Wald *P*-value
Intercept		0.02 (0.0002, 1.54)	0.08
Duration of morning stiffness			
None or <15 min	21 (21)	Reference category	
15 min to 2 h	54 (54)	0.26 (0.08, 0.84)	0.02
>2 h	25 (25)	0.27 (0.09, 0.85)	0.03
Haemoglobin		1.52 (1.07, 2.16)	0.02
CXCL-9		0.98 (0.97, 0.996)	0.009
Therapy during follow-up			
Biologic agents	14 (14)	2.80 (0.96, 8.16)	0.06
Interval between baseline and visit, *y*		2.37 (0.84, 6.69)	0.10
AUC-like statistic			
	Minimum	**Mean**	**Maximum**
Training data	0.79	0.79	0.79
Test data	0.69	0.69	0.69

Included variables showed a univariate $P < 0.1$ and no bivariate correlations (Spearman's $|\rho| \leqslant 0.6$). AUC: area under the curve; CXCL-9: chemokine C-X-C motif ligand 9; GEE: generalized estimating equations; m: number of visits; n: number of patients.

Associations in a prediction model do not prove causality. Nonetheless, the predictors in these models merit further attention. Regarding the model for oligoarticular patients, intuitively it is convincing that patients with higher disease activity at baseline experience decreased odds of achieving inactive disease. Nothing is known about *Mogibacteriaceae* in the context of autoimmune diseases. In our previous analysis, there was no difference in the relative abundance of *Mogibacteriaceae* between JIA patients and healthy children (Van Dijkhuizen *et al.*, manuscript in preparation). *Mogibacteriaceae* were less abundant in obese Japanese people, with respect to lean subjects [36], and a decreased abundance of *Mogibacteriaceae* in the bronchial microbiome of asthmatic subjects has been observed [37].

Regarding the predictors for the polyarticular RF negative and the ANA positive patients, a longer duration of morning stiffness was associated with decreased odds of achieving inactive disease. Notably, this predictor was very consistent in all the algorithms that were employed

Table 5 Best performing GEE model ANA positive patients ($n = 88$)

Parameter	Visits ($m = 298$)	OR (95% CI)	Wald *P*-value
Intercept		0.001 (6.2×10^{-6}, 0.17)	0.008
Duration of morning stiffness			
None	88 (29.5)	Reference category	
<15 min	39 (13.1)	2.16 (0.55, 8.40)	0.27
15 min to 1 h	79 (26.5)	0.78 (0.25, 2.37)	0.66
1–2 h	40 (13.4)	1.52 (0.39, 5.88)	0.55
>2 h	52 (17.4)	0.26 (0.10, 0.69)	0.007
Haemoglobin		1.69 (1.16, 2.46)	0.007
Knee involvement (count)		0.86 (0.49, 1.49)	0.59
Wrist involvement (count)		0.76 (0.43, 1.33)	0.33
Cervical spine involvement	11 (3.7)	0.38 (0.07, 2.21)	0.28
JADAS-71		0.99 (0.93, 1.06)	0.76
Therapy during follow-up			
None	50 (16.8)	Reference category	
IACI ± NSAIDs	56 (18.8)	3.03 (0.99, 9.26)	0.05
MTX ± steroids	151 (50.7)	2.24 (0.79, 6.32)	0.13
Biologic agents	41 (13.8)	6.90 (1.68, 28.41)	0.007
Interval between baseline and visit, *y*		3.83 (1.75, 8.35)	0.0007
AUC-like statistic			
	Minimum	**Mean**	**Maximum**
Training data	0.78	0.79	0.81
Test data	0.71	0.72	0.74

Included variables showed a univariate $P < 0.1$ and no bivariate correlations (Spearman's $|\rho| \leqslant 0.6$). AUC: area under the curve; IACI: intra-articular corticosteroid injections; JADAS: juvenile arthritis DAS; m: number of visits; n: number of patients.

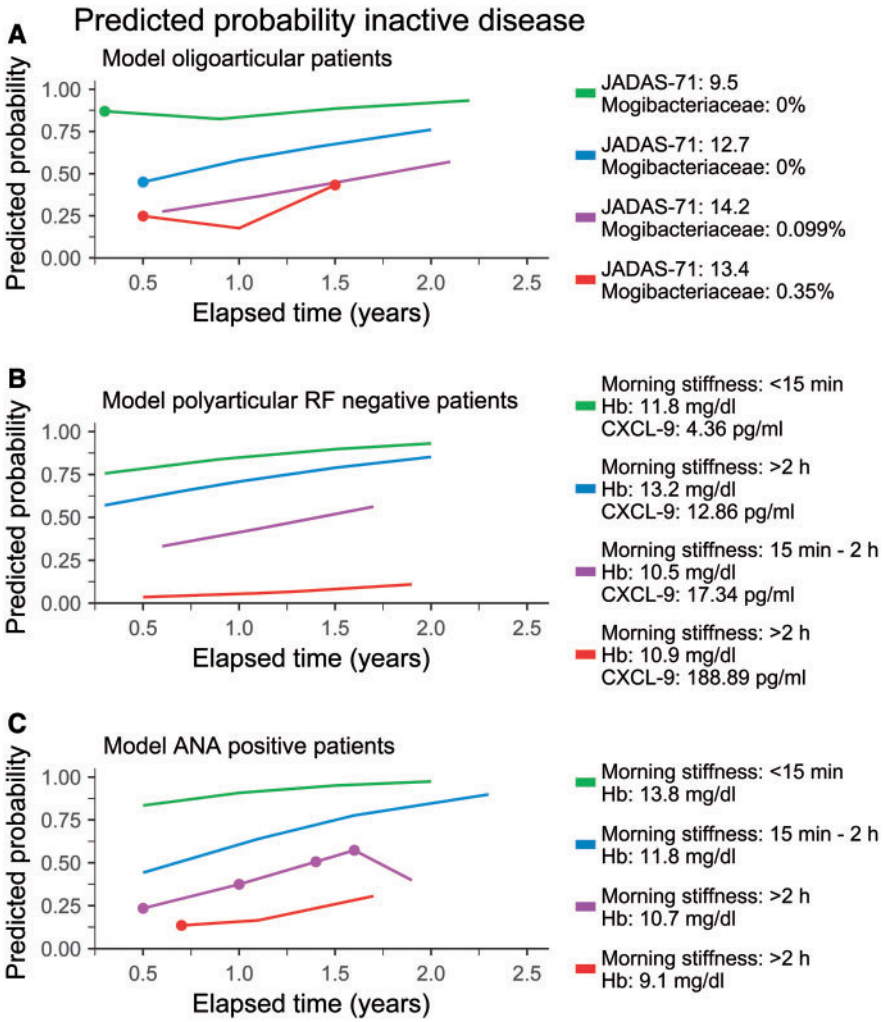
(supplementary Tables S2–S6, available at *Rheumatology* online). In a previous analysis, it was also a determinant of the satisfaction of JIA patients with their current illness condition (Del Giudice *et al.*, manuscript in preparation). These findings highlight the importance of the patient's opinion in the evaluation of disease activity and support the notion of taking their evaluation into account in therapeutic decision-making. Indeed, the value of the clinical JADAS as a criterion for treatment escalation improved when the patient's opinion was fully taken into account [38]. Haemoglobin level was correlated with the ESR and therefore was thought to be reflective of anaemia of chronic disease, making the relationship between a low haemoglobin level and decreased odds of achieving inactive disease convincing.

CXCL-9 is a pro-inflammatory chemokine induced by IFN-γ and is a ligand of CXCR-3. It induces Th1 and 17 cells and recruits these to sites of inflammation. Indeed, CXCR-3 positive cells are highly enriched in the synovium of inflamed joints in RA [39–42] and JIA [43]. Moreover, due to its role in osteoclast activation, it may be involved in the development of bone erosions [44]. In JIA, synovial expression of CXCL-10, another ligand of CXCR-3 with function very similar to CXCL-9, was increased [45, 46]. Taken together, the potential role of this chemokine in the pathogenesis of JIA merits further investigation. The cut-off of 30 pg/ml may be used to identify patients with worse prognosis, but needs validation in future studies.

A recent review of the literature showed that accurate prediction of JIA prognosis using clinical variables alone is unlikely to be achieved [17]. Nevertheless, a clinical prediction model was published recently, showing good predictive performance in test data (AUC: 0.85) [18]. The best AUC of this model was 0.68 in our data, obtained when classifying patients as those who never achieved inactive disease *vs* those who achieved it at least once. However, few patients ($n = 11$) were in the unfavourable category and only one of these was predicted correctly. Thus, these results reinforced the doubts about the prognostic value of clinical data. We are now the first to demonstrate that gut microbiota composition and Luminex data are insufficient to predict JIA prognosis as well. Nevertheless, improved prediction accuracy may be expected when separating JIA patients into more homogeneous subgroups. This finding supports previously made suggestions for a revision of the JIA classification criteria [47–50], and is in line with a recently published report of long-term follow-up of Greek JIA patients showing that JIA is a heterogeneous disease with significant variability in long-term outcome [51].

A limitation of our study is the number of patients and visits with respect to the number of predictors tested. According to some, 40 cases are needed per screened predictor [52]. However, in our situation, this would amount to a cohort of over 10 000 children. It is not feasible to collect full clinical, immunological and gut microbiota data of such a large cohort of JIA patients. Nevertheless, the prediction models developed in the secondary analyses have to be interpreted with caution (especially the model for polyarticular RF negative

Fig. 1 Predicted probabilities of inactive disease



Predicted probabilities of inactive disease during 2 years of follow-up according to the models for oligoarticular (**A**), polyarticular RF negative (**B**) and ANA positive (**C**) JIA patients. Shown are four selected patients with different values for the significant variables in each of the models, illustrating how the predicted probability of inactive disease varies across the values. CIs are not shown, but are very wide, indicating poor precision of the prediction. The circles in (**A**) and (**C**) indicate visits following an intra-articular corticosteroid injection.

patients). Many predictors in the multivariable analysis were not significant. This, coupled with the fact that the number of patients in the subgroups was substantially lower with respect to the full cohort, might indicate that the increased predictive performance was due to overfitting. Further validation and optimization of the models is needed.

In conclusion, the prognosis of JIA could not be predicted accurately in this well-defined cohort of treatment-naïve patients at disease onset, using clinical, imaging, microbiota and Luminex data and a wide array of statistical algorithms. The main impediment to an accurate prediction could be the heterogeneity of the disease and better definition of homogeneous subgroups may lead to improved predictions. Indeed, prediction accuracy improved when analysing oligoarticular, polyarticular RF negative and ANA positive patients separately. The subgroup models showed that the duration of morning stiffness was associated with decreased odds of inactive disease, highlighting the importance of the patients' evaluation of disease activity. Moreover, *Mogibacteriaceae* were associated with lower odds of inactive disease in oligoarticular patients and CXCL-9 in polyarticular patients. Efforts should be directed at validating the prognostic value of this OTU and chemokine and at elucidating their potential role in the pathogenesis of JIA.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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